

## NIEHS-funded researchers discover novel compound that could treat autoimmune diseases

By Sheila Yong

Patients with autoimmune disorders often experience painful side effects of the drugs they take to suppress their immune systems. Now, thanks to NIEHS-funded research, there may soon be a way to avoid these side effects.

In a [study](http://www.ncbi.nlm.nih.gov/pubmed/?term=Benzimidazoisoquinolines) (<http://www.ncbi.nlm.nih.gov/pubmed/?term=Benzimidazoisoquinolines>) published Feb. 19 in the journal PLOS ONE, Nancy Kerkvliet, Ph.D., and Siva Kumar Kolluri, Ph.D., both professors at Oregon State University (OSU), report discovery of a chemical compound that may prevent the immune system of these patients from attacking their bodies, while sparing them from the side effects of currently available drugs. Although studies in human subjects are still required, this chemical may result in a safer alternative to treating autoimmune diseases.

### A targeted approach to taming the immune system

Autoimmune diseases can affect almost any part of the body, resulting in diseases such as colitis, multiple sclerosis, and psoriasis. For patients with these diseases, T cells - cells that normally protect the body from pathogens and infections - become hyperactive and attack tissues and organs.

By screening over 50,000 chemical compounds, [Kerkvliet](http://emt.oregonstate.edu/nancykerkvliet) (<http://emt.oregonstate.edu/nancykerkvliet>) and [Kolluri](http://emt.oregonstate.edu/sivakumarkolluri)

(<http://emt.oregonstate.edu/sivakumarkolluri>) found that one chemical, known as 10-Cl-BBQ, binds to a protein inside the T cells called the aryl hydrocarbon receptor (AhR). The resulting chemical-protein complex then moves into the nucleus and turns on a gene expression process that converts the cells into regulatory T cells (Tregs), which suppressed the immune response.

The researchers then used 10-Cl-BBQ to treat mice with graft-versus-host disease - a condition in which the immune system tries to eliminate foreign cells. They found that treating these mice daily completely suppressed the disease. This observation suggests that 10-Cl-BBQ could also be used in patients who receive stem cell or bone marrow transplants to prevent graft rejection.

### Effect without apparent side-effect

"10-Cl-BBQ is different from other treatments used to suppress the immune system, because it acts directly in the T cells to turn them into regulatory T cells," Kerkvliet said in an OSU [press release](#).

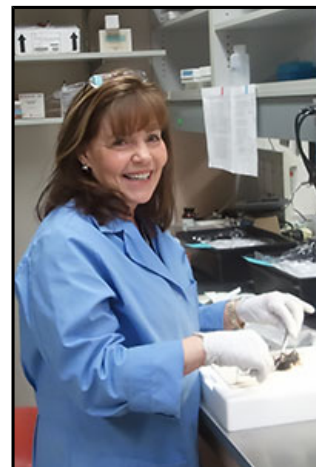
(<http://oregonstate.edu/ua/ncs/archives/2014/mar/osu-finds-new-compound-could-treat-autoimmune-diseases>)

Therefore, she believes that it will cause fewer side effects than currently used drugs. 10-Cl-BBQ is a member of the benzimidazoisoquinoline (BBQ) family, and further analysis of this family of chemicals revealed two other compounds that can induce regulatory T cell formation.

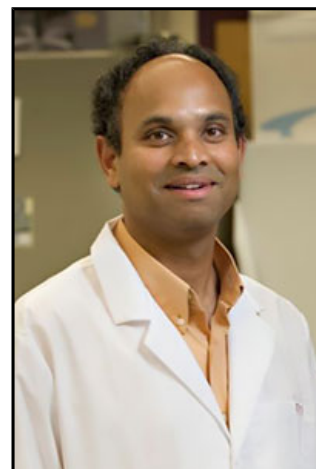
Frederick Miller, M.D., Ph.D., chief of the NIEHS Environmental Autoimmunity Group, believes that the findings from this study have immense therapeutic potential. "These interesting findings, based upon a large body of research implicating the AhR and its pathways as key modulators of inflammation, open up new approaches to the treatment of a wide variety of immune-mediated illnesses," he commented. [Miller](#) said it is important to continue exploring the use of BBQ compounds as treatments for autoimmune disorders and inflammatory diseases, to determine candidates that are best suited for further drug development.

### A surprise discovery from studying a harmful toxin

Kerkvliet has spent most of her career studying a notorious environmental contaminant known as TCDD, or 2,3,7,8-



*Kerkvliet is a professor of immunotoxicology and deputy director of the Environmental Health Sciences Center in the OSU Department of Environmental and Molecular Toxicology. (Photo courtesy of Nancy Kerkvliet)*



*Kolluri, a cancer biologist at Oregon State University, has studied other substances that bind to the AhR protein, recently finding AhR to be a potential target for drug development in liver and stubborn breast cancers (see [story](#)). (Photo courtesy of Nancy Kerkvliet)*

tetrachlorodibenzo-p-dioxin. Interestingly, at the cellular level, 10-Cl-BBQ functions like TCDD. However, unlike TCDD, 10-Cl-BBQ is rapidly broken down and eliminated by the body, which means it can stimulate regulatory T cell formation without harmful side effects. "We spent all these years studying TCDD, because people have been concerned about its presence in the environment," Kerkvliet said. "Yet, look what we have now discovered from those basic toxicology studies."

**Michael Humble, Ph.D.**, NIEHS health scientist administrator who oversees the OSU grant, agrees. "Dr. Kerkvliet's project is a wonderful example of how basic research into the action of a toxic substance can help us understand how a related, but less toxic, chemical may play a role in improving public health."

**Citation:** Punj S, Kopparapu P, Jang HS, Phillips JL, Pennington J, Rohlman D, O'Donnell E, Iversen PL, Kolluri SK, Kerkvliet NI.

(<http://www.ncbi.nlm.nih.gov/pubmed/?term=Benzimidazoisoquinolines>)

2014. Benzimidazoisoquinolines: a new class of rapidly metabolized aryl hydrocarbon receptor (AhR) ligands that induce AhR-dependent Tregs and prevent murine graft-versus-host disease. PLoS One 9(2):e88726. [Summary](#)

(Sheila Yong, Ph.D., is a visiting fellow in the NIEHS Inositol Signaling Group.)

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